REMARKS

Claims 54, 55, 58, and 63 have been amended, and new claims 64-68 have been added. Upon entry of this response, claims 54-55 and 57-68 are pending.

Claim 54 has been amended to recite administering an antigen presenting cell that presents an autoantigen and an anti-gp39 antibody. This amendment is supported by the specification as filed at, *e.g.*, p. 9, l. 34 to p. 10, l. 7, and falls within the subject matter of the claims elected in the response on April 3, 2000 in response to the requirement for restriction mailed on March 1, 2000. Claim 55 has been amended to conform to claim 54, and claim 58 has been amended to correct a typographical error. Claims 55 and 58 have further been amended to correct the spelling of "Langerhan" to "Langerhans'". The misspelling of "Langerhans'" in the specification and in the claims is an obvious mistake. The correct spelling was well known in the art at the time of filing. Claim 63 has been amended to recite that the antigen presenting cell is a peripheral blood activated B lymphocyte. This is supported by, *e.g.*, Example 1 at page 14.

New claim 64 recites that the antigen-presenting cell is an activated bone marrow lymphocyte. This is supported by the specification at, e.g., page 10, lines 35-37 and by Example 1, p. 14. New claim 65 recites that the antigen-presenting cell is a dendritic cell, *i.e.*, a particular species of the antigen-presenting cells recited in claim 55.

New claims 66-68 are directed to the method of claim 54 in which the anti-gp39 antibody is a monoclonal antibody such as MR1, as described, for example, on page 29, lines 4-6; or a chimeric antibody containing human constant regions, as described at, *e.g.*, p. 8, ll. 16-265.

No new matter has been added by way of this amendment. Each of the Examiner's rejections is discussed below.

Obviousness

Claims 54-56 and 58-63 are rejected under 35 U.S.C. § 103 as being unpatentable over Lederman et al. (U.S. Patent No. 6,403,091; "Lederman") or Armitage et al. (U.S. Patent No. 6,264,951, "Armitage") or Aruffo et al. (U.S. Patent No. 6,376,459; "Aruffo") (collectively the "antibody references"), in view of Beschorner et al. (U.S. Patent No. 5,597,563; "Berschorner"), Cobbold et al. (U.S. Patent No. 5,690,933; "Cobbold") and Eynon et al. (1992, "Enyon") (collectively the "tolerization references").

This rejection is respectfully traversed, for the simple reason that no combination of the cited references would have given the skilled artisan any motivation with any reasonable expectation of success to achieve a reduction in T-cell responsiveness to an autoantigen. Consequently, none of the references provide any motivation to administer an antigen-presenting cell and an anti-gp39 antibody.

Assuming for the sake of argument that the references provided the motivation to arrive at the necessary combination, there is no such reasonable expectation of successfully achieving the invention, since (1) the Lederman (to the extent this reference, which is available under 36 USC 102(e), teaches anything about antibodies to gp39/CD40L), Armitage, and Aruffo references describe antibodies or soluble CD40 compounds binding to gp39, and the uses of such antibodies and compounds only teach reducing a B-cell response, and (2) the remaining references describe treatment methods which, while some of them involve APCs and may affect T-cell responsiveness, suggest nothing about or actually teach away from any involvement of gp39/CD40 interactions. The interpretation of the reference combinations suggested by the Examiner must, therefore, be purely based on hindsight reconstruction based on the present disclosure. This practice has been deemed impermissible by the courts:

> It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious. This court has previously stated that "one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.

> Id. (quoting *In re Gorman*, 933 F. 2d 982, 987, 18 U.S.P.Q. 2d 1885 (Fed. Cir. 1991) and *In re Fine*, 837 F. 2d 1071, 1075, 5 U.S.P.Q. 2d 1596, 1600 (Fed. Cir. 1988).

For the very same reasons, *i.e.*, that the "antibody references" are limited to B-cell responses and that the remaining references cannot be applied to the use of anti-gp39 antibodies, there is no motivation to combine references from the different groups.

The Examiner argues that Enyon acknowledges the role of B-cells as APCs; and that it was known that CD40 is present on other APCs such as dendritic cells that are "intimately involved in the induction of T-cell immunity", and that gp39 was known to be expressed mainly by activated Th-cells and by a number of CD8+ cells. The Examiner further argues that Berschorner teaches the use of antigen-presenting cells for inducing tolerance to autoantigens, and that Cobbold teaches that specific non-responsiveness to a self-antigen can be induced by use of "immunosuppressive antibodies". The Examiner then concludes that the prior art provides motivation and expectation of success that (office action, p. 4, 2nd paragraph):

> ... providing an immunosuppressive regimen, including antagonistic antibodies, in combination with APCs can induce tolerance or antigen-specific nonresponsiveness ...

and that Lederman, Armitage, and Aruffo provides antagonists of the "immune response" (office action, p. 4, 3rd paragraph).

As described in the specification, it has been discovered ". . . under appropriate conditions, interference of an interaction between gp39 on a T cell and a ligand [CD40] on a cell which is presenting antigen to the T cell can induce antigen specific T cell tolerance." See page 3, lines 7-10 of the present application. Since nothing on the antibody references suggest that such an effect could be achieved by anti gp39 antibodies, this was a new and surprising finding over the antibody references.

Tolerization References

Contrary to the Examiner's interpretation of the Enyon, Berschorner, and Cobbold references, careful review of each reference, considering what it fairly teaches as a whole, reveals that:

Enyon's T-cells are not activated, and therefore do not express gp39. The Examiner next argues that Enyon teaches that B cell presentation of antigen in the absence of appropriate T cell help leads to antigen-specific T cell anergy. The Examiner contends that Enyon evidences that the idea of tolerance induction taught by Enyon, combined with the knowledge that CD40 is present on other APCs that are "intimately involved in the induction of T-cell immunity", and that gp39 was known to be expressed mainly by activated T_h-cells, renders the present claims obvious.

At page 131, 2nd column, 1st full paragraph, the Enyon reference states (emphasis added): "In this paper, we propose that presentation of antigen by a small, resting B cell to a T-cell is tolerogenic and results in loss of T cell activity". As the Examiner points out (see above), gp39 is only expressed on activated T-cells. Enyon is thereby irrelevant to any tolerization process involving T-cells expressing gp39 since there would be no need to administer an activated T cell inhibitor if T cells never became activated in the first place (due to the lack of co-stimulatory signal).

What is actually taught by Enyon is tolerance induction to a monovalent soluble antigen by resting B cells, i.e., APCs lacking the ability to send a secondary signal to T cells. This induces *temporary* tolerance to the antigen. Enyon further teaches that "**B cells** must be targeted for tolerance to occur" (page 133, col. 1). To achieve this, Enyon simply injects the antigen intravenously into normal mice, and then challenges the mice intraperitoneally a week later with a "more antigenic" form of the same antigen. Specifically, the tolerance taught by Enyon requires use of an adjuvant. Moreover, such *temporary* induction of tolerance to an autoantigen, as described by Enyon, would be fairly worthless from a therapeutic perspective.

The present claims teach a method of inducing T cell tolerance to an autoantigen by administering an APC that presents that antigen with an anti-gp39 antibody. Enyon is silent on the necessity of administering a gp39 antagonist. Indeed, for the reasons presented above, Enyon's teachings are directed to resting B cells. Since B cells do not express gp39, there is no motivation to modify Enyon by introducing anti-gp39 which does not bind to B cells.

Moreover, according to Enyon, the "most straightforward mechanisms for the induction of tolerance by resting B cells would be anergy or deletion of naïve antigen-specific T cells..." (page136, col. 2, second full paragraph). Since Enyon teaches that this tolerance is achieved according to her method, then there would have been no motivation to administer an anti-gp39 antibody (i.e., anti-T-cell antibody) in addition to her method. Again, there is no motivation, and in fact a teaching away, to modify Enyon by administering an anti-gp39 antibody.

Anti-gp39 antibody would have deleterious effects on Berschorner's tolerization process. Berschorner's tolerization process is based on depletion of the dendritic cells (APCs) in the thymic medulla using an immunosuppressant followed by recruitment or infusion of new APCs to the thymus while treating with various stimulating growth hormones etc. (Berschorner, col. 2, ll. 30-45). In this process, the timing of the immunosuppressive treatment and APC recruitment or infusion is critical (Berschorner, col. 5, ll. 13-20):

> The agent should be administered for a period of time long enough to deplete the thymic medulla of those APCs, such as dendritic cells, which are present at the beginning of therapy and is preferably withdrawn before the thymic medulla is repopulated with new APCs which induce tolerance for the antigen. By withdrawing the immunosuppressive agent at this time, deleterious effects of the agent on the new APCs are minimized.

Hence, to avoid deleterious effects, the immunosuppressant should <u>not</u> be present when the new APCs start presenting their antigen or autoantigen to T-cells, with subsequent T-cell activation and gp39 expression. Accordingly, an anti-gp39 antibody (which the Examiner refers to as an alleged "immunosuppressant") would have a deleterious effect in this context, as no gp39 is present

prior to administration of APCs, and once gp39 is expressed (after administration of APCs), there is no longer any anti-gp39 antibody present.

Therefore, Berschorner teaches away from the method of the present claims since Berschorner's method of not administering an immunosuppressant along with the APCs is in direct contravention to the presently claimed method. Both methods are mutually exclusive of each other, the epitome of a teaching away.

In addition, Berschorner's immunosuppressant is cyclosporine A, rapamycin, desoxyspergualine, and FK506 (a rapamycin analog), or functional equivalents. These agents are general immunosuppressants and will suppress the entire immune system while they persist.

Further, there could have been no motivation to combine Berschorner's method of tolerance induction by thymic depletion of dendritic cells using an immunosuppressant (which is not a gp39 antagonist), followed by *APC* (i.e., dendritic cell) administration, with Enyon's tolerance method of *antigen* administration to resting B cells in the presence of an adjuvant (an immunostimulant). Moreover there would have been no motivation to combine these references with Cobbold, who teaches using an anti-CD4 antibody (optionally with an anti-CD8 antibody) to induce T cell tolerance. As discussed below, Cobbold's antibodies are irrelevant to the presently claimed method, and irrelevant to the methods taught by Enyon and Berschorner

Cobbold's teachings are irrelevant to anti-gp39 antibodies. Cobbold describes the use of non-depleting anti-CD4 and anti-CD8 antibodies in eliciting tolerance to an antigen. Antibodies against these targets have long been known to have a direct effect on T-cell viability and to induce immunosuppression (see, *e.g.*, Cobbold, col. 1, ll. 24-45). These teachings cannot, however, be randomly extrapolated to antibodies against any T-cell antigen, particularly to antibodies against gp39 which were believed to only inhibit the T-cell's activation of a B-cell. That the loss of interaction between gp39 and CD40 would also affect the T-cell itself was a novel finding, first

disclosed in the present application, and not in any way suggested by Cobbold or any other reference cited by the Examiner.

Moreover, there would be absolutely no motivation to combine Cobbold with Lederman since Lederman teaches away from using depleting antibodies, including an antibody against CD4. "The mAb OKT4 was selected as an isotype matched control in these experiments because OKT4 reacts with T cell surface CD4 molecules but does not inhibit T-B interactions" (col. 23, ll. 62-66).

Combined Teachings of Enyon, Berschorner, and Cobbold. As outlined above, none of the tolerization processes described in these references could be applied within the context of interfering with gp39/CD40 interaction, since no gp39 would or, indeed, should be present at the same time as anti-gp39 antibody for the Enyon and Berschorner methods to work, and since Cobbold is irrelevant to gp39/CD40 interactions. In addition, there would be motivation to combine since none of the references teach a gp39 antagonist. Absent this teaching, there could have been no motivation to combine these references. Even improper combination of the references would not arrive at the presently claimed method, since, as discussed above, the tolerance methods taught by the three references and the pending claims are vastly different. This is illustrated by a hypothetical combination of the references as follows:

A combination of Enyon and Berschorner would lead one of skill in the art to first administer an autoantigen in combination with an adjuvant, then administer a general immunosuppressant to deplete thymic dendritic cells, then repopulate the thymus with APCs expressing the autoantigen. This clearly would not lead to tolerance induction.

A further combination with Cobbold would lead a skilled artisan to administer an anti-CD4 antibody somewhere in above mish-mash, but not during the repopulation with APCs.

Applicants respectfully submit that this combination is incongruent, and fails to teach the method of the present claims. Applicants respectfully point out that merely identifying references for combination with the appropriate buzzword (i.e., "tolerance"), is improper according to the law, which requires some suggestion or motivation in the references to combine them, and which further

requires the combination to teach the claimed method with some reasonable expectation of success. In this case, neither of these requirements are met.

Antibody References

The Examiner has previously noted that the Lederman, Armitage, and Aruffo (antibody references") do not teach the administration of an autoantigen expressing cell (office action dated 10/22/2002; p. 3, 2nd paragraph), whether in conjunction with antibodies or not. However, what is also missing from each and every one of the anti-gp39 antibody references is a suggestion that anti-gp39 antibodies can have any effect on T-cell responsiveness. Instead, these references only teach that anti-gp39 antibodies may reduce B-cell activation. The following excerpts from each of the three references illustrate the actual teachings of the antibody references (emphasis added):

> These data indicate that the interaction of CD40 with its ligand is the principal molecular interaction responsible for T cell contact dependent induction of B cell growth and differentiation to both antigen-specific antibody production and polyclonal Ig secretion. As such, these data suggest that antagonists of this interaction, by soluble CD40, CD40/Fc fusion protein and possibly soluble CD40-L (monomeric), will significantly interfere with development of antibody responses. Therefore clinical situations where CD40, CD40/Fc fusion proteins and soluble CD40-L are suitable include allergy, lupus, rheumatoid arthritis, insulin dependent diabetes mellitus, and any other diseases where autoimmune antibody or antigen/antibody complexes are responsible for clinical pathology of the disease. (Armitage, col. 31, ll. 42-55).
>
> This invention provides a monoclonal antibody which specifically recognizes and forms a complex with T-B cell activating molecule (T-BAM) (now also known as CD40 ligand) a protein located on the surface of activated T cells and thereby inhibits T cell activation of B cells. (Lederman, col. 2, ll. 15-19).[1]

[1] With respect to Lederman, Applicants further submit that this reference is prior art with respect to the teaching that 5c8 antigen is the same as gp39/CD40L as of its issue date, or at the earliest as of the issue date of US Patent No. 5,474,771. The quoted passage from Lederman was not in the specification as filed; it was added to the specification by an amendment (copy attached at **Tab 1**). There is no suggestion, much less an explicit teaching, in Lederman *as filed* of antibodies to gp39/CD40L, except for the specific antibody, 5c8, disclosed therein. Consequently, there can be no basis for concluding that Lederman teaches the anti-gp39 antibody limitation of the claimed invention, much less suggests the use of such an antibody for the purpose of reducing T cell responsiveness.

> In particular embodiments, the invention provides for a method of treating a subject suffering from a disorder associated with B-cell activation, comprising administering to the subject a therapeutic amount of ligand that binds to CD40CR. (Aruffo, col. 16, ll. 18-22).

None of these references teach inhibiting T cell activation, much less against an autoantigen. Clearly, the references which do disclose autoimmune diseases at all are primarily concerned with inhibition the autoantibody (i.e., humoral) response. By contrast, the object of the present invention is to inhibit the T cells responses. Thus, the latter method is more therapeutically effective since it is the T cell cytotoxic tissue destruction that is the culprit in many autoimmune diseases.

No Motivation to Combine

Without any teaching or suggestion that anti-gp39 antibodies also might affect T-cell responsiveness, there would be no motivation to combine any of Lederman, Armitage, or Arruffo with the "tolerization" protocols described by Enyon, Berschorner, and Cobbold ("tolerization references") in a method to reduce T-cell responsiveness, in particular since basic knowledge of the expression patterns of gp39 would certainly discourage the skilled artisan to use an anti-gp39 antibody in Enyon's or Berschorner's protocols. The Examiner vaguely connects the "immunosuppressive regimens" used in the tolerization references to the "antagonists of the immune response" provided by the antibody references (office action, p. 4, 2nd and 3rd paragraphs); however, "[t]he showing of a motivation to combine must be clear and particular, and it must be supported by actual evidence." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999) (emphasis added).

In this context, it is noted that the "antagonists of the immune response" provided by the antibody references are only described as affecting B-cell activation. Based on the teaching of antibody references, the skilled artisan would not have believed that the "immunosuppressive regimens" described in the tolerization references could be achieved by an anti-gp39 antibody. Accordingly, there is no clear and particular motivation to combine the references as suggested by the Examiner.

No Reasonable Expectation of Success

Even if forcibly combined, however, there would still be no reasonable expectation of success that the combined teachings of an anti-gp39 antibody references combined with the tolerization references would somehow lead to a reduction in T-cell responsiveness, because extrapolating one biological phenomenon to another, *e.g.*, that anti-gp39 antibodies would lead to a reduction in T-cell responsiveness simply because anti-CD4 antibodies do, or simply because they affect B-cell activation, could only be achieved using hindsight reconstruction based on the present disclosure.

Finally, on page 2, 4th paragraph, the Examiner contends that "[i]t was well known in the art at [the] time the invention was made that the provision of signal 1 (antigen) in the absence of signal 2 (help) would lead to some form of tolerance rather than immunity". The Examiner is respectfully invited to provide support for this statement since, as determined by the courts:

> A statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made' " because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a prima facie case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). See also *In re Kotzab*, 217 F.3d 1365,1371,55 USPQ2d 1313,1318 (Fed. Cir. 2000) (Court reversed obviousness rejection involving technologically simple concept because there was no finding as to the principle or specific understanding within the knowledge of a skilled artisan that would have motivated the skilled artisan to make the claimed invention); *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308,50 USPQ2d 1161 (Fed. Cir. 1999) (The level of skill in the art cannot be relied upon to provide the suggestion to combine references.). See MPEP 2143.01.

Additionally, even if the Examiner supports for this statement with evidence, it would not render the presently claimed invention obvious, since, as argued above, there is nothing in any

of the reference combinations suggesting that an anti-gp39 antibody would have any effect on T-cell responsiveness.

Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

If any points remain in issue, the Examiner is respectfully request to contact the undersigned attorney at the telephone number listed below. It is the intent of the undersigned to shortly contact the Examiner to discuss the scheduling of a personal interview to hopefully advance the prosecution of several related cases associated with the present applicant.

Dated: August 27, 2004

Respectfully submitted,

By _____

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Seth Lederman, et al.	
Serial No.	:	07/792,728	Group Art Unit: 1805
Filed	:	November 15, 1991	Examiner: P. Gambel
For	:	MURINE MONOCLONAL ANTIBODY (5c8) RECOGNIZES A HUMAN GLYCOPROTEIN ON THE SURFACE OF T LYMPHOCYTES	

30 Rockefeller Plaza
New York, New York 10112
May 23, 1994

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

AMENDMENT IN RESPONSE TO NOVEMBER 22, 1993 OFFICE ACTION AND PETITION FOR A THREE-MONTH EXTENSION OF TIME

This Amendment is submitted in response to the November 22, 1993 Office Action issued by the United States Patent and Trademark Office in connection with the above-identified application. A response to the November 22, 1993 Office Action was originally due on February 22, 1994. Applicants hereby request a three-month extension of time. The required fee for a three-month extension of time for a small entity is FOUR HUNDRED TWENTY DOLLARS ($420.00) and a check in the amount of $420.00 is enclosed. Applicants have previously established small entity status and it is still applicable. A response to the November 22, 1993 Office Action is now due May 22, 1994. However, since May 22, 1994 is a Sunday, a response filed on May 23, 1994 is timely under 37 C.F.R. §1.7. Accordingly, this Amendment is being timely filed.

Please amend the subject application as follows:

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In the Title:

Delete the title and insert the following new title:

MURINE MONOCLONAL ANTIBODY (5c8) RECOGNIZES T-B CELL ACTIVATING MOLECULE (T-BAM) (CD40 LIGAND) ON THE SURFACE OF T-LYMPHOCYTES, COMPOSITIONS CONTAINING SAME AND METHODS OF USE

In the Specification:

Page 1, line 18 Delete "refernce" and insert --reference--.

Page 1, line 19 After "known" insert --to one--.

Page 4, line 5 After "with" insert --T-B cell activating molecule (T-BAM) (now also known as CD40 ligand),--

Page 12, line 22 Delete "standrad" and insert --standard--.

Page 12, line 28 Delete "Thew" and insert --The--.

Page 32, line 32 Delete "paraformeldehyde" and insert --paraformaldehyde--.

Page 33, line 19 Delete "μCI" and insert --μCi--.

In the Claims:

Please amend claims 8-10 under the provisions of 37 C.F.R. §1.121(b) by inserting the underlined material as follows:

--8. (Amended) A monoclonal antibody of claim 1 capable of binding to the protein to which monoclonal antibody 5c8 (ATCC Accession No. HB 10916) binds.--

--9. (Amended) A monoclonal antibody of claim 1 capable of binding to the epitope to which monoclonal antibody 5c8 (ATCC Accession No. HB 10916) binds.--

--10. (Amended) The monoclonal antibody 5c8 (ATCC Accession No. HB 10916).

REMARKS

Claims 1-12, 17 and 33-34 are pending in this application.

The Title and Specification have been amended according to the suggestion of the Examiner to whom this application is assigned. The Specification has also been amended to correct obvious clerical errors. Accordingly, this amendment does not raise an issue of new matter and applicants respectfully request entry of the amendments.

Applicants acknowledge withdrawal of the rejections of claims 1-12, 17 and 33-34 under 35 U.S.C. §112, first paragraph concerning deposit of biological material and under §112, second paragraph as indefinite.

Applicants acknowledge withdrawal of the rejection of claims 1-3, 17 and 33 under 35 U.S.C. §102(b) over Rogozinski et al.

Applicants acknowledge withdrawal of the previous rejection of claims 1-4, 8-10, 17, 33 and 34 under 35 U.S.C. §102(b) or §103 over Borst et al.

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Applicants acknowledge withdrawal of the rejection of claims 1-7, 11, 12, 17 and 33 under 35 U.S.C. §103 over Weiss et al. in view of Dillman.

Applicants acknowledge withdrawal of the rejection of claims 1-12, 17, 33 and 34 under 35 U.S.C. §103 over the combination of Crow et al., and Hodgkin et al., and Dillman et al.

Applicants acknowledge withdrawal of the rejection of claims 4-7, 11 and 12 under 35 U.S.C. §103 over Rogozinski et al. as applied to claims 1-3, 17 and 33 above and in further view of Dillman.

Applicants acknowledge withdrawal of the rejection of claims 5-7, 11 and 12 under 35 U.S.C. §103 over Borst et al. as applied to claims 1-4, 8-10, 17, 33 and 34 above and in further view of Dillman.

Amendment of Title and Summary

In response to the Examiner's invitation and to expedite the prosecution of this application, the Title and the Summary of the Invention have been amended to refer to the various names by which the 5c8 antigen has come to be called subsequent to applicants' invention, including "T-B cell activating molecule" (T-BAM) and "CD40 ligand" (CD40-L).

Applicants wish to emphasize that 5c8 antigen (described herein as T-BAM) was identified as a cell surface molecule that induces B cell differentiation to Ig secretion. Applicants discovered T-BAM on the basis of its essential role in contact-dependent T helper function and appreciated that pharmacologic intervention utilizing mAbs against this molecule had potential in the treatment of autoimmune diseases and allergic disorders. The murine form of T-

BAM was originally identified and termed CD40-L based on a cDNA clone of a murine protein that bound recombinant chimeric human CD40-Fc fusion protein. At that time, it was not known whether "CD40-L" was a cell surface molecule or a cytokine (secreted molecule). After applicants sequenced T-BAM protein and cloned cDNAs encoding T-BAM, the identity of T-BAM and CD40-L was clearly demonstrated. The rationale for therapeutics based on anti-T-BAM mAbs (such as 5c8) depends critically on the effects that such mAbs may have on antigen specific immune responses including autoimmune and allergic immune responses. This rationale was based on the fact that T-BAM is a cell surface molecule and not on its potential cytokine characteristics. Applicants also wish to point out that the name "CD40 ligand" may be somewhat misleading. For example, T-BAM may interact with molecules besides CD40, and CD40 may have other ligands besides T-BAM. Therefore T-BAM may be a better term because it reflects the unique role of T-BAM in immune physiology and autoimmune and allergic phenomena.

Claimed Invention Possesses Utility

The Examiner rejected claims 1-12, 17, 33 and 34 under 35 U.S.C. §101 on the grounds that the claimed anti-T-BAM antibodies and hybridomas allegedly lack utility as therapeutic agents for inhibiting the immune response or diseases or as diagnostic agents for imaging or detecting T cell tumors in vivo. The Examiner stated that when utility is directed to pharmaceutical compositions which "reads on human therapy," the data must generally be clinical, however, animal data would be acceptable in those instances where one of ordinary skill in the art would accept the correlation to human utility and there exists an art-recognized model for testing purposes. (emphasis added). With regard to human therapy, the Examiner cited Harris et al. as stating that there is widespread acceptance that there is little future for the

use of rodent monoclonal antibodies for in vivo human therapy and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses. The Examiner further stated that humanized antibodies present serious problems with immunogenicity, since the idiotype of such antibodies will contain unique amino acid sequences.

The Examiner objected to the Specification and rejected claims 1-12, 17, 33 and 34 on the grounds that the Specification allegedly fails to provide an enabling disclosure and to set forth the best mode as required under 35 U.S.C. §112, first paragraph. The Examiner indicated that the alleged insufficiency of the written description is based on inoperability of the claimed antibody for therapeutic and diagnostic use as set forth in connection with the rejection under Section 101.

In response, applicants respectfully traverse the rejections of claims 1-12, 17, 33 and 34 under 35 U.S.C. §§101 and 112, first paragraph.

Therapeutic Utility of Murine Antibody

Applicants have already presented in vitro data showing that anti-T-BAM mAb inhibits B cell activation by both Jurkat D1.1 cells (Specification, Example 3 at page 41, line 1 to page 42, line 22) and normal T cells (Specification, Example 7 at page 45, line 19 to page 47, line 20). MR1 is a hamster anti-T-BAM antibody in mouse that is similar to mAb 5c8 with respect to its ability to inhibit contact dependent activation of B cells in vitro. See **Exhibit B:** Noelle, et al., Proc. Nat'l Acad. Sci. - USA (1992) 89: 6550-6554. It is therefore anticipated that both 5c8 and MR1 would have similar biological activities in humans and mice, respectively.

Mouse anti-human T-BAM mAb 5c8 does not bind to mouse T-BAM, and conversely, hamster anti-mouse T-BAM mAb MR1 does not bind to human T-BAM. Therefore, MR1 therapy in mice is analogous to 5c8 therapy in humans. Applicants submit that testing mAb MR1 in a murine model would be accepted in the art as predictive of the effects of mAb 5c8 in humans. As evidence of the acceptance of the murine model, Durie, et al. recognized that the ability of hamster anti-murine-T-BAM mAb MR1 to inhibit inflammation in mice suggests that the "blockade of gp39 [T-BAM] function has potential therapeutic benefits for affecting the onset of autoimmune disease." **Exhibit D:** page 1330. Applicants wish to point out that there are no art-recognized primate autoimmune models, partly for ethical reasons. Because the testing cannot be done in a primate model of autoimmunity, an antibody raised against a non-primate T-BAM, such as MR1 which recognizes mouse T-BAM, is the best available animal model and would be accepted in the art.

Recently, the in vitro data presented by applicants that anti-human-T-BAM inhibits the ability of T cells to direct B cell differentiation has been confirmed in an in vivo animal model. The experiments involved the hamster monoclonal antibody MR1, which was raised against murine T-BAM (gp39). **Exhibit A:** Alfons, et al., J. Exp. Med. (1993) 178: 1555-1565 at 1562, paragraph beginning "Recently". See also, **Exhibit B:** Noelle, et al., Proc. Nat'l Acad. Sci. - USA (1992) 89: 6550-6554; **Exhibit C:** Hollenbaugh, et al., EMBO J. (1992) 11: 4313-4321. In a murine model of human autoimmune disease, anti-murine-T-BAM mAb MR1 was shown to inhibit collagen-induced arthritis. Initially, arthritis was induced in mice by intradermal injection of collagen type II. Then, three groups of eight mice received either no mAb, MR1, or irrelevant hamster Ig (HIg). "A high percentage of the untreated and HIg-treated [control] mice showed extensive distal joint inflammation; none of the anti-gp39-treated mice exhibited any signs of such

inflammation." **Exhibit D:** Durie, et al., "Prevention of collagen-induced arthritis with an antibody to gp39, the ligand for CD40," Science (1993) 261: 1328-1330. The absence of an inflammatory immune response in mice treated with anti-T-BAM antibody demonstrates that anti-T-BAM mMAb, by binding T-BAM and inhibiting its effector functions, effectively inhibited the immune response of mice receiving anti-T-BAM mAb.

The in vivo results demonstrating the therapeutic utility of an analogous anti-T-BAM monoclonal antibody (MR1) supplement the in vitro data that mAb 5c8 inhibits the ability of normal T cells to direct B cell differentiation. See Specification, page 46, line 23 to page 47, line 20; and page 51, lines 26-28. Accordingly, a person of skill in the art would accept the utility of the claimed T-BAM specific monoclonal antibody for therapeutic use.

Based on the biological activity of anti-T-BAM antibodies that prevent T-BAM binding to CD40, it was anticipated that humans with defective T-BAM molecules (i.e., that do not bind CD40) would have defective antibody production. This expectation was confirmed by the results of recent studies involving patients with X-linked immunodeficiency with normal or elevated IgM (HIGMX-1). HIGMX-1 patients have undetectable serum levels of IgG, IgA and IgE. It has been found that the presence of abnormalities in the gene for T-BAM is associated with HIGMX-1. These results demonstrate that the interaction between the B cell antigen CD40 and T-BAM expressed on activated T cells is critical for T cell driven isotype switching and the appropriate generation of antibody responses. B cells in HIGMX-1 patients are blocked at the IgM stage of differentiation because switching from IgM/IgD to other Ig isotypes is inhibited in HIGMX-1 patients, who lack a functional T-BAM. See, **Exhibit E:** Ramesh, et al., Int'l Immunol. (1993) 5: 769-773. These results constitute in vivo evidence that the lack of normal

interaction between T-BAM and CD40 inhibits B cell activation in humans, and provide further support for inhibiting an autoimmune response, such as an inflammatory response or an allergic response, in humans by inhibiting the B cell activating function of T-BAM. The antibody of this invention transiently creates a state which mimics the absence of appropriate antibody production found in HIGMX-1 patients.

Human Therapy using Murine Antibody

It is accepted in the art that murine mAbs against T cell surface molecules do possess utility in human therapy. One such antibody, OKT3, a murine mAb which binds to a T cell surface molecule, has been demonstrated to be effective in the treatment of transplanted allograft rejection and has been approved by the Food and Drug Administration (FDA). See, **Exhibit F:** Physicians' Desk Reference, pages 1594-1596. Accordingly, a person of skill in the art would believe that other monoclonal antibodies against other T cell surface molecules with unique functions (such as T-BAM) are therapeutically useful, and thus provides evidence for acceptance by those skilled in the art of the utility of mAb 5c8, or other monoclonal antibodies against T-BAM, for human therapy.

In addition to the proven utility of a murine antibody anti-T cell surface molecule antibody (OKT3) in human therapy, a person of skill in the art would appreciate that there are several features of applicants' invention which lessen the importance of the concerns identified by Harris. The Harris publication states that there is little future for the use of rodent mAbs for in vivo human therapy for three reasons: (1) the human immune response against murine proteins (HAMA response); (2) very short half-life; and (3) poor recognition of rodent immunoglobulin constant regions by human effector functions. Harris also states that repeated dosing with

2-72

chimeric antibodies is ineffective because of a residual HAMA response.

With respect to the first characteristic identified by Harris, the HAMA response, inhibition of B cell activation by mAb 5c8 renders the HAMA response less limiting to the usefulness of the claimed antibody than of murine mAbs which are not specific for a protein which regulates B cell activation, such as T-BAM which plays a unique and essential role in B cell activation. Murine mAb 5c8, which binds to human T-BAM, inhibits T helper cell activation of B cells, thereby inhibiting the animal's immune response. See Specification, page 18, line 30 to page 20, line 14; and Example 7 at page 45, line 19 to page 47, line 20. By inhibiting the immune response, anti-T-BAM antibodies inhibit the production of antibodies against themselves, as has been demonstrated for the hamster anti-mouse T-BAM mAb MR1 in mice.

This feature of the claimed invention, inhibition of the anti-antibody response, has been confirmed in an animal model that is predictive of the effects of anti-human-T-BAM in humans. Three groups of eight mice received either no antibody, hamster anti-murine-T-BAM mAb MR1, or control hamster antibody (HIg). Whereas HIg elicited a strong immune response, no anti-hamster antibodies were detected in mice treated with MR1. **Exhibit D:** Durie, et al., at 1329 middle column. In another experiment, two groups of three mice received 250 μg hamster anti-murine-T-BAM mAb MR1 (anti-gp39) or 250 μg control hamster antibody (HIg). The anti-hamster antibody response was inhibited greater than 90% in mice treated with MR1 as compared to HIg-treated mice. **Exhibit G:** Foy, et al., J. Exp. Med. (1993) 178: 1567-1575 at 1571. Thus, no anti-anti-T-BAM antibodies were detected. Accordingly, one skilled in the art would understand that mAb 5c8 or other anti-T-BAM antibodies can be administered in a therapeutic regimen that will elicit no

significant HAMA response.

The importance of the interaction between T-BAM expressed on T cells and CD40 on the surface of B cells for an adequate immune response is further confirmed by the results of studies involving patients with X-linked immunodeficiency with normal or elevated IgM (HIGMX-1), as discussed above in connection with general therapeutic utility of the antibody of this invention.

Moreover, it is known in the art to block the HAMA response by coadministering cyclosporin A together with the murine monoclonal antibody. **Exhibit H:** Weiden, et al., Cancer (Supp.) (1994) 73: 1093-1097. Accordingly, even in the event that HAMA responses were induced by mAb 5c8 or by other anti-T-BAM mAbs, this response could be inhibited by one skilled in the art by coadministration of the anti-T-BAM mAb with cyclosporin A.

Even if there would be a HAMA response, the claimed antibody would still be useful in treatment of humans with acute disease. In such cases, an anti-antibody response is not an issue because the antibody will be used in only a single treatment regimen which may include multiple administrations over the course of up to approximately 3 weeks.

With respect to the second characteristic of murine antibodies in humans identified by Harris, short half-life, the half life of anti-T-BAM antibody 5c8 is not so short as to be without therapeutic utility. Furthermore, based on the behavior of MR1 in the murine antibody response to a model peptide antigen, only a small total number of administrations may be required. MR1 had long lasting effects from only a single treatment regimen of three injections in the murine model. Intact serum MR1 could be detected for at least seventeen days after the last administration (twenty-

one days after the initiation of antibody treatment. **Exhibit G:** Foy, et al., figure 1; page 1570, sentence bridging columns, and page 1572, paragraph bridging columns. In a murine model of human autoimmune disease, hamster anti-murine-T-BAM antibody MR1 administered every 4 days prevented all signs of inflammation. **Exhibit D:** Durie, et al. at 1328, right column. See also, **Exhibit G:** Foy, et al. For purposes of illustration, even if the half-life of murine mAb 5c8 in humans is only one day, the frequency of dosing required would constitute an acceptable treatment regimen.

In addition, an ordinary artisan would take the short half-life into consideration and use or modify the antibody appropriately. For example, in one use of the claimed antibody, imaging T cell tumors (Specification, page 20, line 16 to page 21, line 19), short half-life is desirable. Moreover, physicians prescribe drugs with a short or long half-life depending on the treatment objective. In cases where a long half-life is desired, it is known in the art to extend the half-life of antibodies by coupling the antibody to agents with a longer half-life, such as polyethylene glycol (PEG). However, where a short-half life is therapeutically indicated, the physician can prescribe the uncoupled murine antibody.

The third characteristic identified by Harris, poor recognition of rodent immunoglobulin constant regions by human effector functions, does not negate the utility of this invention. The claimed monoclonal antibody binds to T-BAM, thereby inhibiting T cell effector functions. The activity of mAb 5c8, and other anti-T-BAM antibodies, depends on its binding to T-BAM and blocking the interaction of T-BAM with CD40 and not on interactions with human effector functions. Accordingly, while more efficient recognition by human effector functions enhances the efficacy of humanized T-BAM-specific antibody, T cell effector functions are inhibited even without recognition of mAb 5c8's constant region by human effector

functions.

In summary, despite Harris' statements concerning murine monoclonal antibodies generally, applicants submit that a person of skill in the art would understand that a murine monoclonal antibody which binds to a T cell surface protein necessary for B cell differentiation, such as T-BAM, is useful.

Utility of Chimeric Antibodies

In response to the Examiner's position that the chimeric antibody of claim 5 lacks utility because repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic response, please note that the murine experiments found that mice treated with anti- murine T-BAM mAb MR1 did not manifest a humoral immune response to either the idiotype or the Fc region of the hamster MR1 antibody. **Exhibit G:** Foy, et al., figure 3 and paragraph bridging columns; **Exhibit D:** Durie, et al., at 1328 middle column. Thus, anti-murine T-BAM antibody did not elicit an anti-idiotypic response. Accordingly, an anti-idiotypic response against anti-human T-BAM antibodies will not be a serious problem in humans under appropriate dosing conditions.

Applicants further wish to point out that chimeric anti-T-BAM has improved usefulness in human therapy as compared to murine anti-T-BAM because of several desirable characteristics of chimeric antibodies. First, chimeric anti-T-BAM antibody would have been expected to have the advantage of a longer half-life than its murine counterpart. Second, chimeric anti-T-BAM antibody is recognized by and interacts with human effector functions, and therefore elicits a different anti-T-BAM response. For example, a chimeric antibody with an FcγI constant region will bind complement in serum, leading to the death ("deletion") of the T-BAM-expressing

T cells. Alternatively, a chimeric antibody with an FcγIV region interacts with certain Fc receptors on different effector cells. Chimeric antibodies and techniques for making them were within the ability of the ordinary skilled artisan. See Specification, page 11, lines 13-15.

Utility of Humanized Antibodies

In response to the Examiner's position that even humanized antibodies present serious problems with immunogenicity since the idiotype of such antibodies will contain unique amino acid sequences, please note that the murine experiments found that mice treated with anti- murine T-BAM mAb MR1 did not manifest a humoral immune response to either the idiotype or the Fc region of the hamster MR1 antibody. See **Exhibit D**: Durie, et al., at 1328 middle column. Thus, anti-murine T-BAM antibody did not elicit an anti-idiotypic response, which is the only potential anti-antibody response which could limit the usefulness of humanized antibody. Accordingly, an anti-idiotypic response against anti-human T-BAM antibodies will not be a serious problem in humans under appropriate dosing conditions.

The utility of humanized anti-T-BAM antibodies is supported by the success of others in treatment using humanized monoclonal antibodies. For example, monkeys treated with a humanized anti-Tac antibody evoked anti-antibody titers that were five to ten-fold lower than the murine anti-Tac antibody and these antibodies developed later than in the murine antibody-treated monkeys. None of four monkeys developed antibodies after a single treatment with humanized anti-Tac mAb. See, **Exhibit I**: Hakimi, et al., J. Immunol. (1991) 147:1352-1359. Accordingly, using appropriate dosing conditions, humanized antibodies can be used in an effective treatment regimen without a significant anti-idiotypic response.

2-77

Furthermore, the Harris publication considers humanized antibodies to be a solution to the limitations of rodent mAbs, as recognized by applicants. Specification, page 11, lines 15-17. Harris also describes approaches to making humanized Abs that are more "human", and therefore less prone to provoking a HAMA response. See, Harris at page 42, column 3 to page 43, column 2.

Diagnostic Utility

The Examiner alleged that the evidence that mAb 5c8 binds D1.1 Jurkat cells is not convincing in showing that this antibody can be used as a diagnostic reagent to identify T cell tumors and raised the question of how one would distinguish between T-BAM-specific binding of normal cells and tumor cells (November 22, 1993 Office Action, paragraph 32).

In response, T tumor cells are distinguishable from normal T helper cells by location, by the quantity of cells in lymph nodes, and by the quantity of T-BAM molecules they express.

First, with respect to the location of T-BAM expressing cells, "T cell surface protein is formed in animals free of tumors only on the surface of activated T cells ... in the germinal centers of lymph nodes. However, the protein is found on the surface of T cell tumor cells circulating in the blood of the animal." (Specification page 20, lines 29-34). Thus, T-BAM (5c8 antigen) is not expressed on the surface of normal (non-tumor) T cells in the peripheral blood. Accordingly, the presence of T-BAM expressing cells in peripheral blood is diagnostic of an abnormality such as a tumor. Thus, the Specification describes the use of the claimed antibody in detecting and imaging T cell tumors sufficiently to enable a person of ordinary skill in the art to practice these uses without undue experimentation.

Second, there are normally very few T-BAM expressing cells even in the germinal centers of lymph nodes, and normal T-BAM expressing cells express relatively few T-BAM molecules per cell. Accordingly, an elevated number of such cells, or cells that express high amounts of T-BAM is also suggestive of tumors.

Therefore, in view of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejections under Sections 101 and 112, first paragraph.

Claims 5 and 6 are Defined and Enabled

The Examiner rejected claims 5-6 under 35 U.S.C. §112, first and second paragraphs.

In response, applicants respectfully traverse the rejection of claims 5-6 under 35 U.S.C. §112, first and second paragraphs.

The Examiner stated that claims 5-6 are indefinite in the recitation of "chimeric monoclonal antibody" and "humanized monoclonal antibody" because the characteristics of these antibodies allegedly are not known, particularly, which regions of the antibody are chimeric or humanized.

The Examiner also alleged that the specification does not provide a sufficient enabling description of how to make and use chimeric and humanized antibodies which possess high enough affinity for diagnostic and therapeutic procedures.

In response, the chimeric monoclonal antibody of this invention (claim 5) is defined as a "murine monoclonal antibody comprising constant region fragments from a different animal." See Specification page 25, lines 21-25. The term "chimeric monoclonal

antibody" generally means a murine antigen-binding region and a human constant region. Chimeric antibodies were well known in the art and a large number of chimeric antibodies had been made and were found to maintain their antigen specificity. Accordingly, it is well defined from the disclosure which regions are chimeric. With respect to binding affinity, because the antigen binding region is contributed by the variable region of the immunoglobulin molecule, there is no expected change in specificity or affinity by making a chimeric antibody.

The humanized mAb of this invention (claim 6) is defined as a "murine monoclonal antibody in which human protein sequences have been substituted for all the murine protein sequences except for the murine complement determining (CDR) of both the light and heavy chains." See Specification, page 11, lines 25-31. Therefore, humanized 5c8 Ab is all human amino acid residues except for the CDRs, which are derived from 5c8 and provide the binding specificity for T-BAM. Accordingly, it is well-defined from the disclosure which regions are humanized.

Furthermore, applicants submit that it would be within the ordinary skill in the art to generate other chimeric and humanized monoclonal antibodies which bind T-BAM. The mAb 5c8 secreting hybridoma is a source of mRNA encoding mAb 5c8. The sequence of the two antibody chains (heavy and light) can then be determined from isolated cDNA which encodes mAb 5c8. Using these cDNA sequences as a starting point, variant antibodies could be made using standard techniques and antibodies with sufficiently high binding affinities could be identified by comparison with mAb 5c8.

Accordingly, one possessing ordinary skill in the art would be enabled by the Specification to generate, without undue experimentation, other antibodies based on the mAb 5c8 sequence,

including chimeric and humanized antibodies, which also specifically bind T-BAM.

Therefore, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 5 and 6 under 35 U.S.C. §112, first and second paragraphs.

Applicants are the Inventors of Claimed Invention

The Examiner rejected claims 1-4, 8-10, 17, 33 and 34 under 35 U.S.C. §102(f) on the grounds that applicants allegedly did not invent the claimed subject matter. The rejection is based on Lederman, et al., "Identification of a novel surface protein on activated CD4+ T cells that induces contact-dependent B cell differentiation," J. Exp. Med. (April 1992) 175: 1091-1101. The Examiner stated that there is ambiguity as to inventorship because the above-cited publication lists as authors, in addition to the applicants, three individuals who are not named as inventors in the subject application: Alexander Krichevsky, John Belko and Julie J. Lee. The Examiner acknowledged that this publication "says nothing about inventorship." The Examiner stated that applicants must provide a satisfactory showing which would lead to a reasonable conclusion that applicants alone are the inventors of the claimed invention.

In response, applicants respectfully traverse the rejection of the claims under 35 U.S.C. §102(f). The invention claimed in the subject application was conceived solely by applicants and was reduced to practice, either by applicants directly or through persons acting under applicants' direction or supervision.

Alexander Krichevsky provided the SP2/0 fusion partner cell line and assisted applicants with the spleen fusion, an established

laboratory technique.

Both John Belko and Julie Lee worked as laboratory technicians under applicants' direction and supervision.

In view of the foregoing, applicants submit that the rejection under Section 102(f) has been overcome.

Conclusion

In summary, for the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds for objection and rejection set forth in the November 22, 1993 Office Action and earnestly solicit allowance of the claims now pending in the subject application, namely claims 1-12, 17 and 33-34.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone at the number provided.

No fee, other than the $420.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required,

authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this paper is being deposited this date with the U.S. Postal Service as first class mail addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Albert Wai Kit Chan 5/22/94

Albert Wai-Kit Chan Date
Reg. No. 36,479

Summary of the Invention

This invention provides a monoclonal antibody which specifically recognizes and forms a complex with a protein located on the surface of activated T cells and thereby inhibits T cell activation of B cells. This invention also provides the monoclonal antibody 5c8 (ATCC Accession No. HB10916).

This invention provides a human CD4$^-$ T cell leukemia cell line designated D1.1 (ATCC Accession No. CRL 10915) capable of constitutively providing contact-dependent helper function to B cells. This invention also provides an isolated protein from the surface of activated T cells, wherein the protein is necessary for T cell activation of B cells. This invention further provides an isolated, soluble protein from the surface of activated T cells, wherein the protein is necessary for T cell activation of B cells.

Monoclonal antibody 5c8 and a human CD4- T-~~cell~~ cell line, designated, D1.1 have been deposited on November 14, 1997 with the American Type Culture Collection, 12301 Parklawn Drive, Rockville Maryland, 20852, U.S.A, pursuant to the provisions of the Budapest Treaty on the International Recognition of the Microorganism Deposit for the Purposes of Patent Procedure and have been accorded ~~ATCC Accession Nos. and~~ ATCC ACCESSION NOS. HB10916 and CRL10915 respectively.